Using an Animal Model of Deficient Sensorimotor Gating to Study the Pathophysiology and New Treatments of Schizophrenia

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Abstract

Certain animal models can greatly enhance our understanding of the neurobiology of schizophrenia and can be used to predict the antipsychotic activity of compounds. Prepulse inhibition (PPI), the reduction in startle produced by a prepulse stimulus, is diminished in schizophrenia patients. Theoretically, deficient PPI in schizophrenia patients is a measure of the loss of sensorimotor gating that may lead to sensory flooding and cognitive fragmentation. In rats, PPI is disrupted by systemic administration of dopamine agonists, serotonin agonists, or glutamate antagonists and by a variety of surgical or pharmacological manipulations of neural circuitry linking the limbic cortex, striatum, pallidum, and pontine reticular formation. This article describes several different ways the loss of PPI in rats can be used as a model for studying the pathophysiology and neurobiology of impaired sensorimotor gating in schizophrenia patients and for predicting antipsychotic activity in novel compounds. First, new experimental strategies may be used to distinguish behavioral profiles of "typical" versus "atypical" antipsychotics. Second, this paradigm can be used to study the effects of early developmental insults—including neonatal lesions and isolated rearing—on the adult emergence of deficient sensorimotor gating. Third, using different animal strains and species, as well as gene "knockout" strategies, greatly increases our ability to understand specific genetic or receptor contributions to the regulation of deficient PPI. Each of these uses of the PPI paradigm is enhanced by studies of the basic brain substrates that regulate PPI in rats and by the increasingly sophisticated assessments of PPI and related measures in schizophrenia spectrum patients.

Key words: Animal models, antipsychotics, prepulse inhibition, sensorimotor gating.

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The startle reflex is a constellation of responses to sudden, relatively intense stimuli and is usually classified as a defensive response. For more than 50 years, the startle reflex has been studied systematically as a means of understanding the neural control of simple behaviors. One major advantage of startle response paradigms is that the same phenomena can be studied across many species. In humans, the blink reflex component of the startle response is measured using electromyography of the orbicularis oculi muscle. In rats, a stabilimeter chamber is used to measure the whole-body flinch elicited by stimuli similar to those used in human studies. Davis et al. (1982) reported a "primary" mammalian acoustic startle circuit, now thought to consist of three synapses linking the auditory nerve with the spinal motor neuron. The relatively simple startle reflex also demonstrates several conceptually important forms of behavioral plasticity—including habituation and fear potentiation (Davis 1984)—that are regulated by forebrain circuitry. Even these more complex processes exhibit striking similarities across species ranging from rodents to humans (Geyer and Braff 1987; Grillon et al. 1994). One form of startle plasticity is prepulse inhibition (PPI), which is the normal suppression of the startle reflex when the intense startling stimulus is preceded by a weak prestimulus (Hoffman and Searle 1968; Ison et al. 1973; Graham 1975) (figure 1).

In PPI, a weak prepulse inhibits a reflex response to a powerful sensory stimulus. PPI occurs when the prepulse and startling stimuli are in the same or different sensory modalities. Virtually all mammals, including primates, exhibit PPI. It is not a form of conditioning, since it occurs on the first exposure to the prepulse and pulse stimuli, and it does not exhibit habituation or extinction over multiple trials. While the inhibitory effect of the pre-

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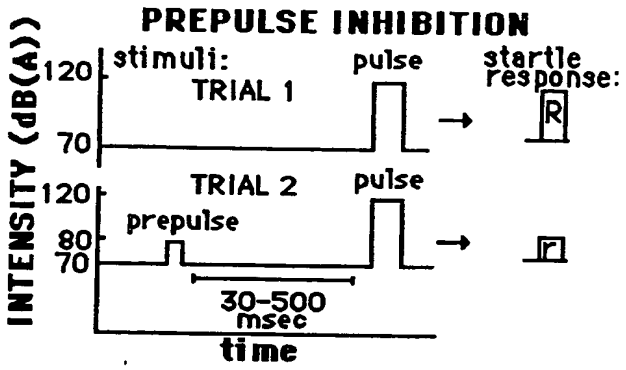
Figure 1. Prepulse inhibition (PPI) of the acoustic startle reflex



Compared to trials on which the startle reflex is elicited by an acoustic pulse alone (TRIAL 1), reflex amplitude is reduced significantly if the acoustic pulse is preceded 30–500 ms by a weak prepulse (TRIAL 2). The degree to which the prepulse inhibits the motor response to an intense sensory stimulus provides an operational measure of sensorimotor gating.

pulse on startle reactivity is undoubtedly exerted in the pons (Davis and Gendelman 1977), studies have described the descending limbic cortico-striato-pallido-pontine influences that regulate inhibitory tone within the pons, and thus determine the degree to which the prepulse inhibits the subsequent motor response (see below). PPI thus appears to reflect the activation of ubiquitous "hard-wired" centrally mediated behavioral gating processes regulated by forebrain neural circuitry.

Interest in PPI as a measure of sensorimotor gating grew from the observation that human disorders with known dysfunction in brain substrates that regulate PPI are accompanied by evidence of impaired cognitive or sensorimotor inhibition. Our laboratory and others have reported deficient PPI in patients with schizophrenia (Braff et al. 1978; Grillon et al. 1992; Bolino et al. 1994; Hamm et al. 1995), obsessive compulsive disorder (Swerdlow et al. 1993), Huntington's disease (Swerdlow et al. 1995*c*), nocturnal enuresis and attention deficit disorder (Ornitz et al. 1992), and Tourette's syndrome (Swerdlow et al. 1994*b*; Castellanos et al. 1996). Conceptually related deficits in the habituation of startle are also observed in patients with schizophrenia (Geyer and Braff 1982; Bolino et al. 1992; Braff et al. 1992). These disorders are all characterized by a loss of gating in sensory, motor, or cognitive domains, and by abnormalities in cortico-striato-pallido-pontine circuitry that modulates PPI and habituation. Note that PPI deficits are not unique to a single form of psychopathology. Instead, these deficits are the result of abnormalities within a specific brain circuit.

It can be hypothesized that both clinical signs and reduced PPI in several disorders result from the same underlying neural deficit. While much more work is needed to address this issue, studies have shown that PPI deficits in schizophrenia patients correlate significantly with neuropsychological measures as distinct as perseverative responses on the Wisconsin Card Sorting Test (WCST) (Butler et al. 1991) and pathologically elevated thought disorder (Perry and Braff 1994). In one recent study, reduced PPI in schizophrenia patients correlated significantly with certain clinical indices of illness severity, including the number of hospitalizations, chlorpromazine equivalents, and global scores of negative symptoms (Braff et al. 1995). PPI is also significantly reduced in nonpatient controls who have a Minnesota Multiphasic Personality Inventory (MMPI) profile associated with specific neuropsychological deficits (Swerdlow et al. 1995*a*). Thus, there is reason to believe that PPI is a measure of sensorimotor gating abilities that may correlate with, and perhaps contribute to, important determinants of information processing in both patients and nonpatient controls. Thus, it is likely that PPI can be used to study the neural circuitry that regulates normal cognitive processes and is defective in several distinct neuropsychiatric disorders.

PPI may be a particularly valuable model for the study of the neural substrates of schizophrenia, because of the relevance of gating anatomy to the pathophysiology of schizophrenia and also because deficits in gating cognitive and sensory information are recognized to be clinically important features of this disorder. Clinical observations in schizophrenia patients have identified deficiencies in sustained or "voluntary" attention and have also identified an inability to automatically filter, or gate, irrelevant thoughts and sensory stimuli from intruding into conscious awareness (McGhie and Chapman 1961). Deficits in PPI and startle habituation in schizophrenia patients do not simply result from gross behavioral impairment or medications, since schizotypal patients who are not grossly psychotic or receiving antipsychotic medications also show both PPI and habituation deficits (Cadenhead et al. 1993). While we do not know the precise substrates of these PPI and habituation deficiencies, neuroimaging and neuropathological studies have revealed abnormalities at several levels of the startle gating circuitry in schizophrenia patients, including the hippocampus (HPC), nucleus accumbens (NAC), striatum, globus pallidus, and thalamus (Bogerts et al. 1985, 1990; Jakob and Beckmann 1986; Altshuler et al. 1990; Pakkenberg 1990; Suddath et al. 1990; Weinberger et al. 1992; Bogerts 1993; Silbersweig et al. 1995).

Over the past 15 years, studies have delineated some of the cortical and subcortical substrates that control PPI in rats. Many of these substrates are implicated in models

for the pathophysiology of neuropsychiatric disorders, including schizophrenia. Specifically, PPI is regulated by cortical-subcortical interactions that are proposed to underlie the emergence of schizophrenia symptoms following early developmental dysfunction in portions of the limbic cortex. Studies of the neural regulation of PPI in laboratory animals and healthy and disordered human populations have grown exponentially over the past three decades. Six studies of PPI were listed in *Index Medicus* between 1966 and 1984; 18 were listed between 1985 and 1989; and 87 were listed between 1990 and mid-1995. These studies extend well beyond the use of this measure to understand the neural connectivity of cortico-striato-pallido-thalamic (CSPT) circuitry.

In humans, PPI is being used as a phenotypic marker in genetic linkage analysis studies in schizophrenia patients (Byerley et al. 1989) and as a probe in studies of correlated regional metabolic activity measured by positron emission tomography in schizophrenia patients (Hazlett et al. 1995). PPI has also been studied productively in several different neurological disorders (Morton et al. 1994, 1995), in drug-challenge studies (Karper et al. 1994; Morton et al. 1995), and in studies of antipsychotic efficacy (Wu et al. 1992). In neurodevelopmental studies of animals, PPI has been found to be a revealing measure, using isolation rearing (Geyer et al. 1993; Varty and Higgins 1995) and neonatal lesion techniques (Lipska et al. 1995). PPI is being studied at a genetic level using strain analyses (Bullock et al. 1996; Ellenbroek et al. 1995*a*) and gene knockout strategies in mice (Dulawa et al. 1995; Grandy et al. 1995). It is used extensively as a model that predicts activity for both D_4 antagonists (Cassella et al. 1994) and atypical antipsychotic agents (Swerdlow and Geyer 1993*a*; Bakshi et al. 1994; Johansson et al. 1994; Swerdlow et al. 1994*c*, 1996; Bakshi and Geyer 1995). In this article, we review studies that have identified some of the physiological substrates regulating PPI. We then discuss several distinct uses of PPI that have emerged from the convergence of studies of the physiology of PPI, as well as those related to evolving hypotheses of the pathophysiology and treatment of schizophrenia.

Physiology and Pharmacology of PPI

The Limbic Cortex. Significant changes in PPI follow experimental manipulations of at least three limbic cortical subregions in the rat: the HPC, the medial prefrontal cortex (MPFC), and the basolateral amygdala (BLA). The specific manipulations of the HPC, MPFC, and BLA that result in a loss of PPI are consistent with existing models for the role of limbic cortical regions in the pathophysiology of schizophrenia.

The HPC. The HPC has been implicated in the control of complex behaviors and emotional states. Further, developmental abnormalities in this region have been implicated in the pathophysiology of schizophrenia (Jakob and Beckmann 1986; Suddath et al. 1990; Weinberger et al. 1992). Specifically, studies have reported reduced HPC volume (Altshuler et al. 1990; Suddath et al. 1990; Weinberger et al. 1992), and abnormal cytoarchitecture (Conrad et al. 1991), metabolism (Weinberger et al. 1992; Silbersweig et al. 1995), and electrophysiology (Adler et al. 1982; Siegel et al. 1984) in patients with schizophrenia. Similarly, studies in twins discordant for schizophrenia have identified HPC abnormalities only in the affected twin (Suddath et al. 1990).

Electrophysiological evidence supports the hippocampal regulation of sensory gating (Adler et al. 1982; Siegel et al. 1984) and is consistent with suggestions that this structure contributes significantly to the neural control of central inhibitory mechanisms (Izquierdo 1975). Some evidence for the involvement of the HPC in regulating PPI has been found in humans: PPI is significantly reduced in patients with temporal lobe epilepsy (TLE) and psychosis, compared to TLE patients without psychosis (Morton et al. 1994).

More substantial evidence for the hippocampal regulation of PPI comes from animal studies. We reported that infusion of the cholinergic agonist carbachol into the HPC reduces or eliminates PPI, but that carbachol infusion into the overlying parietal cortex does not (Caine et al. 1991, 1992). This carbachol effect results from muscarinic receptor activation, since it is reversed by coinfusion of the antimuscarinic atropine (Caine et al. 1991). Carbachol infusion into the HPC disrupts PPI of both acoustic and tactile startle, suggesting that the HPC modulation of PPI is not modality specific (Caine et al. 1991). This HPC cholinergic regulation of sensorimotor gating may be a normal function of the septohippocampal projection, since PPI is reduced by α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA)-induced activation of the septal nucleus; this effect is reversed by intra-HPC infusion of atropine (Koch 1995). Cholinergic activation of the HPC may impair PPI by stimulating glutamate release in the NAC via HPC-NAC glutamate fibers, as suggested by observations that PPI is disrupted by intra-NAC infusion of glutamate (Swerdlow et al. 1992*b*) or the glutamate agonists *N*-methyl-D-aspartate (NMDA) (Reijmers et al. 1995; Wan et al. 1995*b*) or AMPA (Wan et al. 1995*a*), and by reports that intra-HPC carbachol infusions cause behavioral activation that is blocked by intra-NAC infusion of glutamate antagonists (Mogenson and Nielsen 1984). PPI is also disrupted by NMDA infusion into the ventral subiculum, and this effect is reversed by coinfu-

sion of the NMDA antagonist D,L-amino-5-phosphonovaleric acid (APV) (Wan et al. 1996*a*).

A direct link between the hippocampal and ventral striatal regulation of PPI is suggested by findings that ibotenic acid lesions of the HPC in adult rats result in the development of "supersensitivity" to the PPI-disruptive effects of the dopamine (DA) agonist apomorphine (Swerdlow et al. 1995*b*). Other studies suggest that the supersensitive apomorphine disruption of PPI is mediated via the ventral striatum (see below). When hippocampal lesions are made in neonatal (day 7) rats, this apomorphine supersensitivity is not evident until postpuberty. This finding is consistent with existing developmental hypotheses regarding the pathophysiology of schizophrenia (Lipska et al. 1995).

The MPFC. Studies have identified metabolic (Weinberger et al. 1992) and cellular (Benes et al. 1991; Bogerts 1993) abnormalities in the prefrontal cortex in schizophrenia, which are thought by some to result from a consequence of HPC dysfunction (Weinberger 1991, 1995). Prefrontal hypodopaminergia has also been implicated as a critical feature of the neural circuit disturbances that accompany this disorder (Csernansky et al. 1993). In rats, the MPFC potently regulates PPI in a fashion that is consistent with these clinical observations. Thus, PPI is reduced by interventions that decrease MPFC DA "tone," such as depletion of MPFC DA by infusion of 6-hydroxydopamine (6OHDA) (Bubser and Koch 1994; Koch and Bubser 1994), or intra-MPFC infusion of the D_1 or D_2 antagonists SCH 23390 or sulpiride (Ellenbroek et al. 1995*a*). It has been proposed that reduced MPFC DA transmission disrupts PPI via disinhibition of descending glutamatergic fibers, which results in subcortical increases in DA transmission in the NAC. Such a model is consistent with the finding that the PPI-disruptive effects of MPFC 6OHDA lesions are blocked by systemic injection of haloperidol (Koch and Bubser 1994). Also consistent with this model, cellular lesions of the MPFC result in the development of supersensitivity to the PPI-disruptive effects of the DA agonist apomorphine, perhaps via the loss of a descending tonic facilitatory influence on subcortical DA activity (Swerdlow et al. 1995*b*).

The BLA. Compared to the HPC and MPFC, relatively less is known about the regulation of PPI by the BLA. The central nucleus of the amygdala has been implicated in the regulation of fear-potentiated startle in a series of elegant experiments by Hitchcock and Davis (1991). Lesions of the central nucleus of the amygdala disrupt fear-potentiated startle, as do lesions all along the caudal ventral amygdalofugal pathway. Thus, the modulation of startle by conditioned fear is regulated by a pathway connecting the amygdala with the pontine tegmentum.

A recent report by Decker et al. (1995) demonstrated that large radiofrequency lesions of the amygdala significantly reduced PPI. In these studies, prestimuli that elicited a 70 percent suppression of startle in sham-lesioned rats, elicited only a 20 percent reduction in startle in amygdala-lesioned rats. The amplitude of the basal startle response was not significantly modified by these lesions. Given the large size of these lesions, the authors did not attribute these effects on PPI to damage in any specific amygdala subregion.

Studies in our group have recently demonstrated that small, cell-specific quinolinic acid lesions of the BLA potently reduce PPI (Wan and Swerdlow 1996*b*); the magnitude of this lesion effect was consistent with that reported by Decker et al. (1995). These lesions, which were largely restricted to the BLA, did not significantly reduce basal startle amplitude. However, these BLA lesions significantly disrupted fear-potentiated startle, raising the possibility that two structurally different forms of startle modulation—that produced by phasic 20-ms duration acoustic prestimuli (the PPI) and that produced by a "tonic" state of fear elicited by a 4-sec visual cue (fear potentiation)—may share some overlapping neural substrates. Our studies in progress are examining the similarities and differences between the neurochemical and anatomical regulation of these two forms of startle plasticity.

DA Systems. Dysfunction in DA systems has long been implicated in the pathophysiology of schizophrenia, either as a primary locus of action (Snyder 1973) or as a secondary result of prefrontal or limbic-cortical dysfunction (Weinberger 1991; Csernansky et al. 1993). Evidence for the DA hypothesis of schizophrenia includes the observation that effective antipsychotics block DA (D_2) receptors, that all centrally active D_2 antagonists examined thus far are effective antipsychotics (Creese et al. 1976), and that amphetamine intoxication often is accompanied by symptoms that mimic some forms of schizophrenia (Snyder 1973). Studies also report abnormalities in patients with schizophrenia in the number of D_2 family receptors (Seeman et al. 1984; Wong et al. 1986) and the ventral striatal cells that support them (Pakkenberg 1990).

In rats, PPI is reduced by drugs that facilitate DA activity, including the direct DA agonist apomorphine (Swerdlow et al. 1986, 1991, 1994*a*; Mansbach et al. 1988; Schwarzkopf et al. 1992, 1993; Swerdlow and Geyer 1993*a*; Hoffman and Donovan 1994) and the indirect DA agonists *d*-amphetamine (Mansbach et al. 1988; Swerdlow et al. 1990*c*; Wan et al. 1995*b*) and cocaine; these effects are reversed by DA receptor antagonists (Mansbach et al. 1988; Swerdlow et al. 1991, 1994*a*; Schwarzkopf et al. 1993; Swerdlow and Geyer 1993*a*). As

in patients with schizophrenia (Braff et al. 1992), the apomorphine-induced disruption of PPI is not modality specific, but is seen when acoustic prepulses are used to inhibit either acoustic or tactile startle (Geyer et al. 1990). The D_2 receptor may mediate the apomorphine disruption of PPI, since this effect of apomorphine is blocked by the D_2 antagonists raclopride and spiperone (Swerdlow et al. 1991). Further support for a role of the D_2 receptor, but not the D_1 receptor, as a primary substrate of PPI is the finding that PPI is disrupted by the D_2 agonist quinpirole, but not by the D_1 agonist SKF 38393 (Peng et al. 1990; Wan and Swerdlow 1994; Wan et al. 1996*a*). Evidence in our laboratory (Peng et al. 1990; Wan et al. 1996*b*) and others (Hoffman and Donovan 1994) suggests that D_1 and D_2 receptors may interact in the regulation of PPI, but does not suggest that D_1 receptors serve as an independent substrate for changes in PPI. The apomorphine disruption of PPI is reversed by the atypical antipsychotic clozapine (Swerdlow et al. 1991; Swerdlow and Geyer 1993*a*), which lacks neuroleptic properties in some behavioral assays, and the putative atypical antipsychotic quetiapine fumarate (Swerdlow et al. 1994*c*). We reported that the ability of antipsychotics to normalize startle gating in apomorphine-treated rats correlates significantly with their clinical efficacy ($r = 0.99$) (Swerdlow et al. 1994*a*). Recently, it was reported that the putative D_4 antagonist NGD 94-1 restores PPI in apomorphine-treated rats, despite the fact that it is inactive in traditional preclinical measures of antipsychotic action (Cassella et al. 1994). Thus, there is converging evidence for the important involvement of dopaminergic systems, acting via D_2 family receptors, in the control of PPI. These findings in rats parallel the deficits in PPI observed in schizophrenia patients (Braff et al. 1978, 1992), which are also reported to be corrected by both typical and atypical antipsychotics (Wu et al. 1992; Hamm et al. 1995).

Studies of the regulation of PPI by forebrain dopaminergic terminal regions have focused on the nucleus accumbens and the anteromedial striatum.

The NAC. Neural activity in HPC, amygdala, and prefrontal cortex regulate behavior at least in part via their subcortical projections to the NAC and to the cells in the ventral tegmentum that are the source of DA for the NAC (Nauta et al. 1978; Kelley and Domesick 1982; Fuller et al. 1987; Groenwegen et al. 1987; Totterdell and Smith 1989; Heimer et al. 1991; Johnson et al. 1994; Totterdell and Meredith 1997). Thus, within the NAC, there is a convergence of glutamatergic fibers from the HPC, MPFC, amygdala, and cingulate gyrus and of dopaminergic fibers originating from cells in the ventral tegmentum. As such, the NAC is a key subcortical integrative hub, connecting forebrain and limbic structures that control cognition and behavior (Swerdlow and Koob 1987).

Several studies suggest that the effects of DA agonists on PPI are mediated in part by increased DA activity in the NAC. First, low doses of apomorphine that do not decrease PPI in control rats potently disrupt PPI in rats that are surgically altered to have supersensitive DA receptors in the NAC (Swerdlow et al. 1986). Second, the loss of PPI induced by the indirect DA agonist amphetamine is reversed by depletion of DA in the NAC (Swerdlow et al. 1990*c*). Third, PPI is disrupted in rats by infusion of the D_2 agonist quinpirole or DA into the NAC or anteromedial striatum (but not the orbital cortex, amygdala, or posterior striatum) (Swerdlow et al. 1992*b*; Wan et al. 1994). The effects of intra-NAC quinpirole or DA infusion on PPI are reversed by systemic treatment with D_2 antagonists (Swerdlow et al. 1994*a*; Wan and Swerdlow 1994). Fourth, in vivo microdialysis studies of DA levels in the NAC during startle testing have demonstrated that startling stimuli produce a decrease in dialysate DA in the NAC and that this decrease is blocked by prepulse stimuli (Humby et al. 1996). Thus, overactivity of NAC DA may be a substrate for the loss of PPI produced by systemic administrations of DA agonists in rats.

This is not to say that the NAC is the only region of dopaminergic receptors or dopaminergic activity that regulates PPI. In fact, dopaminergic activity in other areas—including the anteromedial striatum—is thought to regulate PPI (see below). Furthermore, it has not been demonstrated that selective blockade of DA receptors within the NAC reverses the PPI-disruptive effects of systematically administered DA agonists. In other words, there is no clear evidence that the neuroleptic restoration of PPI in apomorphine- or quinpirole-treated rats reflects the action of these neuroleptics within the NAC. In fact, our unpublished studies suggest that this might not be the case; the effective dose of haloperidol needed to restore PPI in apomorphine-treated rats is very similar, whether the haloperidol is administered subcutaneously or directly into the NAC (or the MPFC, ventral hippocampus, caudate nucleus, or substantia nigra) (Hart et al. 1996). Obviously, the site of action of neuroleptics in restoring PPI in DA-agonist-treated rats might be very relevant to the use of this measure in the development of antipsychotic agents.

The convergence within the NAC of descending limbic cortical glutamatergic fibers and ascending dopaminergic projections from the midbrain creates a mechanism by which forebrain DA activity can regulate the passage of information as it descends from the limbic cortex and progresses through reverberating CSPT circuit loops (Swerdlow and Koob 1987). The NAC is functionally heterogeneous, with lateral core and medial shell subregions characterized by distinct neurochemical, anatomical, and behavioral properties (Groenwegen et al. 1991; Heimer et

al. 1991). For example, glutamatergic fibers from the dorsal subiculum primarily innervate the lateral NAC core, while fibers from the ventral subiculum primarily innervate the medial NAC shell (Groenwegen et al. 1987). The complexity of this nucleus is magnified by the presence of multiple DA and glutamate receptor subtypes, along with numerous other neurotransmitters and neuropeptides (Groenwegen et al. 1991).

It may be possible to use PPI to characterize the neural connections in the NAC. This approach has been used to examine the interactions between dopaminergic and non-NMDA glutamatergic activity in the NAC that regulate PPI in rats. This work has demonstrated that the dopaminergic regulation of PPI is distributed across the NAC; for example, PPI is reduced by quinpirole infusion into any one of several different NAC locations, with only a small potency gradient favoring lateral core over medial shell regions (Wan et al. 1994). The same is true of the regulation of PPI by non-NMDA receptors in the NAC: AMPA infusion into either the NAC core or shell subregions reduces PPI (Wan et al. 1995*a*; Wan and Swerdlow 1996*a*). In contrast, interactions between DA and glutamate substrates regulate PPI only within the lateral NAC core region, but not within the medial NAC shell. Within the NAC core, the PPI-disruptive effects of AMPA are DA dependent: they are blocked by either 6OHDA lesions or systemic haloperidol injections (Wan et al. 1995*a*). In contrast, the PPI-disruptive effects of intrashell AMPA infusion are not reversed by DA blockade (Wan and Swerdlow 1996*a*). These results suggest that, within the NAC core, activation of non-NMDA receptors causes a reduction in PPI via a facilitatory effect on presynaptic DA release. Such a mechanism is consistent with our findings that blockade of non-NMDA glutamate receptors in the NAC core with 6-cyano-7-nitro-quinoxaline-2,3-dione (CNQX) prevents the PPI-disruptive effects of intra-core infusion of the DA releaser amphetamine (Wan et al. 1995*a*). This effect is also restricted to the NAC core subregion: intrashell infusion of amphetamine reduces PPI, but this effect is not opposed by coinfusion of CNQX (Wan and Swerdlow 1996*a*). Thus, in contrast to the NAC core, within the NAC shell, DA and non-NMDA glutamate transmission appear to regulate PPI independently.

While it is clear that this work is in its infancy, these studies suggest that there is promise in this investigative approach where PPI can be used as a functional measure to examine complex anatomical and neurochemical properties of the NAC infrastructure.

The anteromedial striatum. DA activity in striatal areas other than the NAC also appears to regulate sensorimotor gating. First, PPI is disrupted by low doses of apomorphine in rats with surgically induced supersensitive DA receptors in the striatum (Swerdlow et al. 1986). Supersensitivity to the PPI-disruptive effects of apomorphine is also suggested by studies of patients with Parkinson's disease (Morton et al. 1995). Second, intra-NAC DA infusions disrupt PPI far less than do peripherally administered DA agonists (Swerdlow et al. 1990*b*, 1992*b*, 1994*a*), suggesting that NAC DA overactivity alone cannot account for the PPI deficits produced by systemic DA agonists; DA infusion into the anteromedial striatum also significantly disrupts PPI (Swerdlow et al. 1992*b*). Third, Huntington's disease patients experience a loss of Spiny I gamma-aminobutyric acid (GABA) cells that form the striato-pallidal efferent projection (Reynolds and Pearson 1990). These Spiny I GABAergic cells normally form a lateral inhibitory matrix that is proposed to regulate the promotion or "switching" of cognitive and motor information passing through the striatum via cortico-striatal efferents (Groves 1983). Huntington's disease patients show profound deficits in PPI of both acoustic and tactile startle (Swerdlow et al. 1995*c*), as do rats that have sustained quinolinic acid lesions of the dorsal posterior striatum (Kodsi and Swerdlow 1995). Thus, studies of sensorimotor gating using the PPI model have demonstrated utility in both human and animal studies of basal ganglia and limbic functions, as well as disorders associated with perturbations of these systems.

Other Forebrain Neurotransmitter Substrates of PPI. The major neurotransmitter used by cortico-striatal efferents is glutamate (Fuller et al. 1987), and ascending serotonergic fibers innervate much of the limbic cortex (Joyce et al. 1993). Both forebrain glutamatergic and serotonergic systems have been implicated in the pathophysiology of schizophrenia and the action of atypical antipsychotics (Davis et al. 1991; Joyce et al. 1993; Meltzer 1995). Likewise, both glutamatergic and serotonergic activity are important substrates modulating PPI in rats.

Glutamate. PPI is reduced or eliminated in rats by systemic administration of noncompetitive NMDA antagonists, such as phencyclidine (PCP), dizocilpine (MK-801), and ketamine (Mansbach and Geyer 1989, 1991). As with apomorphine or schizophrenia, both intramodal and cross-modal PPI are sensitive to noncompetitive NMDA antagonists (Geyer et al. 1990). In humans, this class of drugs produces symptoms that mimic some features of schizophrenia (Javitt and Zukin 1991). Furthermore, ketamine has been shown to reduce PPI in normal control subjects (Karper et al. 1994), providing some validation of the similar animal studies. The central locus of action for these effects of systemically administered PCP and dizocilpine are currently under investigation. Our preliminary evidence (above) suggests that NMDA agonists disrupt PPI after infusion into the ventral subiculum, while NMDA antagonists disrupt PPI after

infusion into the basolateral amygdala (Wan and Swerdlow 1996*b*). In studies by others, PPI is also reduced by infusing high doses of NMDA antagonists into the NAC core subregion (Reijmers et al. 1995). Recent studies in our laboratory suggest that the PPI-disruptive effects of PCP are reversed by the atypical antipsychotics clozapine (Bakshi et al. 1994; Swerdlow et al. 1996), olanzapine (Bakshi and Geyer 1995), and quetiapine fumarate (Swerdlow et al. 1996), but not by haloperidol (Geyer et al. 1990; Keith et al. 1991; Swerdlow et al. 1996) or selective D_1 or D_2 antagonists (Bakshi et al. 1994) (see below).

Serotonin 5-HT. PPI is reduced in rats by systemic treatment with 5-HT releasers, including 3,4-methylenedioxy-*N*-methyl amphetamine, 3,4-methylenedioxy-*N*-ethyl amphetamine, fenfluramine, and alpha-ethyltryptamine (Mansbach et al. 1989; Kehne et al. 1992, 1996; Martinez and Geyer 1997), direct 5-HT_{1A} agonists such as 8-hydroxy-dipropylaminotetralin (Rigdon and Weatherspoon 1992; Sipes and Geyer 1994, 1995*a*), and by direct agonists for 5-HT_{1B} and 5-HT_2 receptors (Sipes and Geyer 1994). The effects of 5-HT_{1B} agonists on PPI in rats are reproduced by the administration of a 5-HT_{1D} agonist in the guinea pig, suggesting a functional behavioral homology in the roles of these receptors across species (Sipes and Geyer 1996). This observation further indicates the utility of PPI measures for cross-species comparisons. The PPI-disruptive effects of 5-HT releasers are prevented by pretreatment with the 5-HT reuptake inhibitor fluoxetine, which prevents the drug-induced release of 5-HT from presynaptic terminals (Kehne et al. 1992, 1996; Martinez and Geyer 1997). The PPI-disruptive effects of direct 5-HT_2 receptor agonists, including hallucinogens such as 2,5-dimethoxy-4-iodoamphetamine, are blocked by pretreatment with nonspecific 5-HT_2 antagonists (Sipes and Geyer 1994) or the selective 5-HT_{2A} antagonist MDL 100907 (Padich et al. 1996), but not by a 5-HT_{2C} antagonist (Sipes and Geyer 1995*b*) or by the DA blocker haloperidol (Padich et al. 1996). The 5-HT_{2A} antagonist is also effective in blocking the effects of 5-HT releasers on PPI (Padich et al. 1996). Such findings have contributed to the current investigation of MDL 100907 as a putative nondopaminergic antipsychotic for patients with schizophrenia.

NAC-Subpallidum GABAergic Projection. Decreased PPI after NAC DA activation might reflect reduced activity in GABAergic fibers projecting from the NAC to the subpallidal regions that include the ventral pallidum and the substantia innominata. This striato-pallidal projection thus forms the next segment of a pervasive neural circuit regulating central inhibitory mechanisms in mammals (Mogenson and Nielsen 1984). Some studies also suggest abnormalities in metabolism (Early et al. 1987) and cell number (Bogerts et al. 1985) in the ventral or internal pallidum in schizophrenia patients. The PPI-disruptive effects of NAC DA infusion or cell lesions of the NAC in rats are reversed by infusion of the GABA agonist muscimol into the subpallidum and are reproduced by subpallidal infusion of the GABA antagonist picrotoxin (Swerdlow et al. 1990*a*; Kodsi and Swerdlow 1994). This NAC-subpallidal GABAergic projection is a substrate for other behavioral effects of NAC DA activation and may translate the effects of activity in the HPC to lower motor circuitry. These findings illustrate the potential for the PPI model to enable systematic studies addressing functional connections between different brain structures.

Subpallidal Efferents to the Pedunculopontine Nucleus (PPN). While it is not yet clear how decreased subpallidal GABA activity is translated to the primary startle circuit to modulate PPI, one possible route is via subpallidal efferents to the PPN. We reported that electrolytic or quinolinic acid lesions of the PPN eliminate PPI in rats (Swerdlow and Geyer 1993*b*; Kodsi and Swerdlow 1997), as does muscimol infusion into the PPN (Kodsi and Swerdlow 1997). Recent reports suggest that there are cytoarchitectural abnormalities in the PPN in some schizophrenia patients (Karson et al. 1991), and developmental dysfunction in this region is thought to occur in patients with nocturnal enuresis, who also exhibit reduced PPI (Ornitz et al. 1992). The PPN innervates the nucleus reticularis pontis caudalis (NRPC); electrophysiological studies have demonstrated that the NRPC is responsible for the elicitation of startle responses (Davis et al. 1982).

Summary: Cortico-Striato-Pallido-Pontine Circuitry and Sensorimotor Gating. PPI is a quantifiable measure of complex sensorimotor inhibitory processes that are modulated by a well-characterized neural circuit connecting limbic cortical regions and subcortical dopaminergic systems, and ultimately innervating pontine circuitry via subpallidal efferent projections. Abnormal interactions between the limbic cortical and subcortical elements of this circuitry are proposed in several models to underlie the emergence of clinical symptoms in schizophrenia. Specifically, structural or metabolic abnormalities in schizophrenia patients have been reported at every level of this startle gating circuit, including the HPC, MPFC, striatum, pallidum, and pontine tegmentum. Also, on a broader level, these circuit dynamics seem to underlie the normal development of critical cognitive and behavioral processes. The value of neural circuit analyses using PPI as a dependent measure is evident in the tremendous amount of information generated by this model regarding

complex neurochemical and neuroanatomical features of limbic cortico-striato-pallido-pontine circuitry.

Using PPI in Predictive Models for "Typical" and "Atypical" Antipsychotics

Most predictive models for antipsychotic agents, such as the reversal of apomorphine-induced canine emesis (Freedman and Giarman 1956; Creese et al. 1976) and rodent stereotypy (Creese et al. 1976), assess the ability of a compound to reverse a physiological (behavioral) effect of a DA agonist. Many DA receptor antagonists identified in this manner are clinically useful "typical" antipsychotics that are highly effective in reducing hallucinations and delusions—the positive symptoms of schizophrenia. Indeed, clinical findings (Pickar et al. 1986) and theoretical models (Swerdlow and Koob 1987) link these positive psychotic symptoms to functional hyperdopaminergia, which may result from changes in DA release (Snyder 1973; Pickar et al. 1986) or DA receptor number (Wong et al. 1986) in forebrain regions. In contrast, negative or deficit psychotic symptoms—affective flattening, alogia, or avolition—are linked theoretically to reduced forebrain glutamate transmission (Davis et al. 1991; Javitt and Zukin 1991). Some evidence indicates that these deficit symptoms respond to atypical, but not typical, antipsychotics (Kane et al. 1987). These atypical antipsychotics, such as clozapine, are also associated with a much lower risk for acute Parkinsonian side effects, and to date, no data firmly link the use of clozapine alone to the development of tardive dyskinesia, a common and severe side effect of typical antipsychotic agents. Unlike the ready availability of animal models to predict the antidopaminergic properties of typical antipsychotics, no animal model has convincingly demonstrated such predictive validity for identifying agents with atypical antipsychotic properties. For example, clozapine fails to reverse amphetamine- and apomorphine-induced stereotypy in rats or apomorphine-induced emesis in dogs (Creese et al. 1976).

As discussed above, the ability of antipsychotics—including the prototypic atypical antipsychotic clozapine—to restore PPI in apomorphine-treated rats strongly correlates with their clinical potency ($r = 0.99$) (Swerdlow et al. 1992*a*, 1994*a*; Swerdlow and Geyer 1993*a*). In addition to its sensitivity, the specificity of the PPI model for compounds with antipsychotic efficacy is supported by previous reports that it predicts no such efficacy for buspirone, diazepam, imipramine, naloxone, and propranolol (Rigdon and Viik 1991). We previously reported that another putative atypical antipsychotic agent, quetiapine fumarate restores PPI in apomorphine-treated rats with a potency roughly equivalent to that exhibited by clozapine in this paradigm (Swerdlow et al. 1994*c*). Thus, the PPI paradigm appears to be sensitive to both typical and atypical antipsychotics, but, when used with the DA agonist apomorphine, this paradigm clearly fails to make the potentially important distinction between these two classes of antipsychotic agents.

In addition to its disruption by DA agonists, PPI is also reduced or eliminated in rats by the psychotomimetic noncompetitive glutamate antagonist PCP. However, unlike the effects of DA agonists on PPI, those of PCP are not reversed by typical antipsychotics such as haloperidol (Geyer et al. 1990; Keith et al. 1991) but are reversed by the atypical antipsychotics clozapine (Bakshi et al. 1994), olanzapine (Bakshi and Geyer 1995), quetiapine fumarate (Swerdlow et al. 1996), and remoxipride (Johansson et al. 1994). These findings raise the possibility that the PCP disruption of PPI might be a useful model for identifying compounds with atypical antipsychotic potential. Such predictive validity might be accompanied by construct validity, since PCP-induced clinical and glutamatergic neurochemical effects have been linked to the characteristics and pathophysiology of deficit symptom schizophrenia.

We recently compared the ability of four compounds to restore PPI in PCP-treated rats: haloperidol, clozapine, quetiapine fumarate and risperidone (Swerdlow et al. 1995*b*, 1996). In this work, we replicated the ability of clozapine to restore PPI in PCP-treated rats (Bakshi et al. 1994), as well as the failure of haloperidol to restore PPI in PCP-treated rats (Keith et al. 1991). Interestingly, quetiapine fumarate was extremely potent in reversing the PPI-disruptive effects of PCP, while risperidone was ineffective in this same measure. All four compounds restored PPI in apomorphine-treated rats in subsequent experiments. If this PCP paradigm is a valid model for predicting atypical antipsychotic effects, then these data would predict atypical properties for clozapine and quetiapine fumarate, but not haloperidol or risperidone. It should be noted, however, that Varty and Higgins (1995) reported risperidone, but not clozapine, effective in reversing the PPI-disruptive effects of dizocilpine, which shares many of the glutamate-antagonist properties of PCP. Thus, the pharmacology of this paradigm and its ability to predict atypical antipsychotic properties still require much study.

There are somewhat conflicting clinical data regarding the atypical characteristics of risperidone, with evidence suggesting that, despite the relative lack of acute extrapyramidal side effects with lower doses of risperidone, these side effects are common with higher doses (Dickson et al. 1994; Radford et al. 1995). Furthermore, cases of tardive dyskinesia have now been associated with this drug (Kopala and Honer 1994; Addington et al.

1995). As more clinical data become available, it is possible that the side-effect profile of risperidone may be revealed to be consistent with that of other typical antipsychotic agents. The apparent failure of risperidone to restore PPI in PCP-treated rats is particularly interesting, since risperidone and quetiapine fumarate have significant serotonergic receptor antagonism in common, suggesting that the simple addition of 5-HT receptor blockade to DA receptor blockade does not suffice to create an atypical antipsychotic profile in this paradigm. This finding adds to our previous report (Bakshi et al. 1994) that neither ritanserin nor ketanserin restore PPI in PCP-treated rats.

Using PPI in Models for Neurodevelopmental Processes Relevant to Schizophrenia

Sensorimotor gating deficits in schizophrenia patients, unlike PPI deficits in apomorphine-treated rats, are not an acute drug response, but instead reflect longitudinal and complex interactions of genetic, developmental, social, and environmental forces. For this reason, it is important that startle gating in rats appears to be sensitive to these same forces. Studies also indicate that developmental perturbations significantly alter startle gating in rats. For example, recent studies (Geyer et al. 1993) indicate that isolation-reared rats that exhibit elevated NAC DA activity also demonstrate a neuroleptic-reversible deficiency in PPI compared to group-reared controls. This effect of isolation rearing appears to be developmentally specific, in that similar isolation of adult rats failed to produce the deficit in PPI observed in isolation-reared rats (Wilkinson et al. 1994).

These studies of the effects of isolation rearing on PPI have been extended significantly by Varty and Higgins (1995). In their studies, isolation rearing significantly reduced PPI, and this effect was reversed by typical antipsychotics (haloperidol, raclopride) and atypical antipsychotics (clozapine) and risperidone. Our preliminary findings support the sensitivity of this paradigm to atypical antipsychotics, including olanzapine and quetiapine fumarate (Bakshi et al., in press). Thus, PPI deficits in isolation-reared rats may be a valuable paradigm that, like the apomorphine-induced disruption of PPI, is sensitive but not specific in its ability to identify compounds with atypical antipsychotic properties.

Developmental issues may be particularly relevant to understanding PPI deficits in humans; as PPI appears to develop in children ages 5 to 8 (Ornitz et al. 1990), it is conceivable that abnormal developmental processes may contribute to PPI deficits in adult schizophrenia patients. In one finding of direct relevance to neurodevelopmental theories of schizophrenia (Weinberger 1987), we have noted impaired PPI and enhanced sensitivity to the PPI-disruptive effects of apomorphine in postpubescent rats that had received neurotoxin lesions of the hippocampus as neonates (Lipska et al. 1995). It will be critically important to identify the peripubertal neural circuit changes that occur in neonatal hippocampal-lesioned rats that are responsible for the development of this supersensitive DA-mediated loss of PPI in adulthood. Thus, using strategies that involve either manipulations of the rearing environment or neonatal limbic cortical circuitry, PPI studies can potentially examine the contribution of developmental processes to the pathophysiology of sensorimotor gating deficits in schizophrenia and identify compounds with potential atypical antipsychotic properties.

Using PPI in Genetic Studies: Strain Analyses and "Knockout" Strategies

Genetic factors may also be critical determinants of sensorimotor gating in rats, since strain-related differences in the dopaminergic modulation of PPI have been reported (Rigdon 1990). Other researchers have begun to systematically characterize differences in startle response properties in approximately 50 different rat strains (Glowa and Hansen 1994). If susceptibility to the gating-disruptive effects of DA agonists is genetically controlled in rats, these studies might offer critical insight into genetic factors mediating the susceptibility to, and development of, schizophrenia in humans (Weinberger 1987).

Several new lines of investigation have advanced our understanding of the genetic regulation of PPI. One strategy applied by Ellenbroek et al. (1995*b*) used pharmacogenetic inbreeding to produce strains of rats whose behavior was either apomorphine-sensitive (APO-SUS) or apomorphine-insensitive (APO-UNSUS). Male and female rats were identified from each generation that exhibited the most APO-SUS or least APO-UNSUS gnawing in response to 1.5 mg/kg apomorphine. Within a single generation, APO-SUS rats exhibited significantly less PPI than did APO-UNSUS rats, particularly when weak prepulses were used.

Rats were also studied that were part of a longstanding breeding program, in which APO-SUS and APO-UNSUS rats were inbred for multiple generations. PPI was measured in rats from the 17th and 18th generations of this breeding strategy. Rats descended from an inbred APO-SUS strain exhibited significantly less PPI, compared with rats descended from an inbred APO-UNSUS strain, and this difference was also particularly evident when weak prepulses were used. Apparently, the physio-

logical substrates that regulate the behavioral sensitivity to apomorphine (presumably some feature related to DA receptor sensitivity) are associated with substrates that regulate PPI, and these substrates are transmitted genetically. APO-SUS rats have elevated numbers of striatal D_2 receptors (Cools et al. 1994) and increased responsivity of both the hypothalamic-pituitary adrenal axis (Rots et al. 1995) and dopaminergic systems (Cools et al. 1994). The inheritance of reduced PPI might reflect the expressed inheritance of any one, or a combination of several, of these characteristics.

The use of PPI paradigms in mice has received attention in part because of the advances in molecular biology that rely on murine models. In mice, robust PPI is readily demonstrated, as is a wide range of pharmacological effects on PPI (Dulawa and Geyer 1996). Using a classical genetic approach, Bullock et al. (1996) have begun to study inheritance patterns of PPI characteristics in mice. In these preliminary studies, PPI was compared among seven mice strains, and the strains with the highest (C3H/2Ibg) and lowest (DBA/2J/Ibg) levels of PPI were inbred. A quantitative analysis of inheritance revealed that PPI, but not startle amplitude per se, followed a pattern consistent with dominant transmission. Among the seven different strains, PPI levels did not correlate with one physiological marker—the nicotinic receptor binding in the hippocampus.

Another genetic strategy has been applied to understanding the normal physiological substrates regulating PPI (Dulawa et al. 1995). PPI was compared between wild-type mice and mice that had been genetically engineered to lack 5-HT_{1B} receptors—so called 5-HT_{1B} "knockouts" (5-HT_{1B}KOs). Basal PPI was slightly, but significantly elevated in 5-HT_{1B}KOs compared to wild-types, supporting a tonic regulation of PPI by 5-HT_{1B} receptors. Furthermore, PPI was significantly reduced in wild-type mice by the 5-$HT_{1A/1B}$ agonist RU24969, but RU24969 did not reduce PPI in 5-HT_{1B}KOs. This experimental approach demonstrates the clear use of applying genetic knockout techniques toward understanding the physiological substrates of behaviors and processes such as sensorimotor gating. Similar strategies are currently being applied toward understanding the dopaminergic substrates of PPI using D_4 knockout mice (Grandy et al. 1995).

Summary

The animal studies of PPI have been primarily aimed at understanding the basic physiological and pharmacological substrates regulating sensorimotor gating. This effort has been motivated in part by the awareness that several neuropsychiatric disorders are characterized both by deficits in PPI and by clinical evidence of impaired inhibition of cognitive, sensory, or motor information. The convergence of information from preclinical and clinical studies has supported the notion that brain regions frequently implicated in the pathophysiology of these disorders—the limbic cortex, ventral striatum, pallidum, and pontine tegmentum—are also the substrates that critically regulate PPI. This paradigm has thus been used effectively to study the normal physiology of this important gating circuitry, applying the sophistication of anatomical and pharmacological manipulations to parse complex neural circuit interactions, such as the DA-glutamate interactions within different subregions of the ventral striatum. In the process, it has also been possible to identify the particular perturbations of normal brain function at each level of this circuitry that might yield deficits in PPI, such as those observed in schizophrenia and other disorders, and conversely, what interventions might act at each level of the circuitry to enhance or restore normal levels of sensorimotor gating. Presumably, this functional gating circuit map will become increasingly valuable, as neuroimaging and neuropathological findings draw us closer to identifying the specific brain disturbances associated with these disorders.

In concert with work examining the physiology and pharmacology of PPI, studies have examined several other applications of this model. While several groups have reported the use of PPI as a measure to predict typical neuroleptic properties, recent studies suggest that only atypical antipsychotics restore PPI in PCP-treated rats. This model is still relatively new, but findings at least suggest the possibility that the restoration of PPI can be used as a sensitive measure (with apomorphine) to identify compounds with both typical and atypical antipsychotic properties and as a specific measure (with PCP) to identify only those compounds with atypical antipsychotic properties. Another variant of this model, examining the ability of compounds to restore PPI in isolation-reared rats, appears to be sensitive to both typical and atypical antipsychotic agents.

Genetic studies have applied several strategies to explore the PPI model, from pharmacogenetics, to classical inheritance analysis, to receptor knockout technologies. It is clear that information from this work will become increasingly valuable as PPI and related measures are used as phenotypic markers for genetic linkage analyses in schizophrenia (Byerley et al. 1989) and other disorders. Knockout strategies add a valuable new level of analysis for confirming and extending our understanding of the role of particular physiological substrates, such as the 5-HT_{1B} and D_4 receptors, in the regulation of PPI. It is apparent that PPI is a behavioral measure with a wide range of applications—from neural circuit analyses to

drug development—that can be successfully studied at the level of its physiology, pharmacology, neurodevelopment, and molecular genetics.

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